that diverse methods of MR imaging are patentable. See for example, USP 5,938,599 (Rasche) entitled "MR method and arrangement for carrying out the method." The first claim recites "[a]n MR method of determining positions of and images of a region surrounding an object introduced into a body to be examined in order to monitor a movement of the object in the body. . . ." See also, for example, USP 5,828,215 (Boettcher) entitled "Method for phase contrast MR angiography, and arrangement for carrying out the method." The first claim of this patent recites "[a] method for spatially resolved flow acquisition . . . ." Applicants' invention pertains to methods of monitoring protein denaturation and tissue viability using MR imaging.

Applicants note that the Examiner has rejected claims in the parent application under 35 U.S.C. §112 first paragraph, 35 U.S.C. §102(a), 35 U.S.C. §102(b), 35 U.S.C. §102(e), and 35 U.S.C. §103. Applicants assert that the amended claims filed herewith obviate these rejections as discussed below.

Rejections under 35 U.S.C. §112, first paragraph

The Examiner has previously rejected claims stating that IEMs defined as organic molecules, salts and chelates, particles, clusters, labeled peptides, proteins, polymers, and liposomes are not reasonably enabled. None of the amended claims include a reference to IEMs. Furthermore, the amended claims are all method claims that employ contrast agents comprising "a physiologically compatible, chelated paramagnetic metal ion" (pg. 14, lines 16-19). Applicants assert that contrast agents with chelated paramagnetic metal ions are fully enabled and that a rejection under 35 U.S.C. §112 first paragraph is therefore inappropriate.

Rejections under 35 U.S.C. §102(a) and (e)

Applicants note that "invalidity by anticipation requires that the four corners of a single, prior art document describe *every* element of the claimed invention, either expressly or inherently, such that a person of ordinary skill in the art could practice the invention without undue experimentation." *Advanced Display Systems, Inc. v. Kent State University* 212 F.3d 1272, 1282 (Fed. Cir. 2000) (emphasis added). Further it is noted that "in relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic *necessarily* flows from the teachings of the applied prior art." *Ex parte Levy* 17 USPQ2d 1461, 1464 (Bd.Pat.App.&Int.1990) (emphasis added).

The Examiner has previously rejected claims that were based on the present specification as being anticipated by McMurry (WO 96/23526) stating that "McMurry discloses a method of contrast-enhanced diagnostic imaging comprising administering a contrast agent which is within the scope of the instant claims." Applicants note that the amended claims in the present continuation application (1) do not recite specific contrast agents, (2) recite a monitoring method, not a method of MR imaging, and (3) encompass the novel feature that image enhancement (i.e. relaxivity of the contrast agent) is dependent on the state of the target, namely that image enhancement decreases as tissue viability is lost or as protein denaturation increases. Applicants have for the first time developed a method for measuring protein denaturation and tissue viability using MR imaging with targeted contrat agents. Applicants assert that this method is novel and therefore not anticipated by any prior art reference.

The present claims are directed toward methods for

monitoring protein denaturation and tissue viability not disclosed or contemplated by any prior art reference. The Examiner previously asserted that "[i]t is inherent that methods of diagnostic imaging are used to monitor a specific tissue (e.g., a tumor) that has undergone interventional therapy to determine the effectiveness of the therapy." However, McMurry only discloses contrast agents useful in determining the location of tumors using a "method for monitoring blood flow into . . . tumors." (pg. 6, lines 2-3). McMurry states that "[t]he applications for [the present] type of agent include . . . perfusion (determining the rate of blood flow into a tissue or tumor using rapid imaging)" (pg. 22, lines 28-31). All of the references to the imaging of tumors in McMurry pertain to methods for monitoring blood flow.

The methods of the present invention for monitoring protein denaturation and tissue viability, by contrast, do *not* measure blood flow. The present invention relates to methods for monitoring protein denaturation and tissue viability by measuring the changes in relaxivity that accompany changes in binding between the contrast agent and the target of the agent. Thus, McMurry does not disclose monitoring based on direct changes in the binding properties of contrast agents and a §102 rejection over McMurry is inappropriate.

Rejections under 35 U.S.C. §102(b)

The Examiner has previously rejected claims that were based on the present specification as being anticipated by Brixner (USP 5,094,848). The Examiner relied on the disclosure of column 15 to assert that Brixner "teaches a combined method of MRI and interventional therapy." However, the monitoring methods of the present continuation application are distinguished in that they are not

therapeutic methods themselves like those disclosed in Brixner. The present methods are diagnostic and allow contemporaneous monitoring of interventional therapies. Brixner teaches that "this invention will be applicable to essentially any therapeutic agent (or combination of agents, e.g., known polymers having multiple (the same or different) pendent active agent molecules as discussed above) which can be linked to the [phosphate or amidated phosphate] linker of this invention . . . ." (col. 17, lines 4-10). Brixner lists a number of moieties that can be incorporated into the contrast agents, such as a "cytotoxic drug" (col. 15, line 58), "the antitumor agent Ara-C" (col. 16, line 4), other anti-tumor agents (col. 17, line 10-14), or toxins (col. 17, lines 17-28). Brixner specifically notes that attachment of such moieties results in "therapeutic agents" (col. 17, lines 15-16). Thus, Brixner teaches contrast agents but does not disclose diagnostic methods for monitoring interventional therapies.

Moreover, Brixner does not teach state-dependent binding; Brixner only teaches methods of targeting the specific compounds disclosed within that invention. Brixner does not disclose methods for contemporaneous monitoring of therapies. The present methods correlate a decrease in image enhancement (as measured by the accompanying decrease that in relaxivity) to the extent to which the proteins become heat or chemically denatured. For example, the methods of the present invention allow monitoring of the dramatic 75% decrease in binding that occurs when a protein thermally denatures (see Figure 1) and the dramatic 80% decrease in binding that occurs when a protein chemically denatures (see Figure 3). Brixner has no teaching of a method for monitoring protein denaturation or tissue viability. Thus, Applicants assert that the methods of the present application are novel and not anticipated by

Brixner.

Rejections under 35 U.S.C. §103

The Examiner has previously rejected claims that were based on the present specification as being unpatentable over McMurry (WO 96/23526) and Brixner (USP 5,094,848) and Lauffer (USP 5,250,285) in view of Vogl. As stated above, the present continuation application claims a method for monitoring protein denaturation and tissue viability which includes the non-obvious ability to monitor tissue damage by signal characteristics that arise from the state-dependent binding of the contrast agent. MPEP 2141 states:

> (A) The claimed invention must be considered as a whole;
> (B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;
> (C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention and
> (D) Reasonable expectation of success is the standard with which obviousness is determined.

The consistent criterion for the determination of obviousness is whether the prior art would have suggested to one of ordinary skill that the claimed subject matter should be carried out and would have a reasonable likelihood of success. Both the suggestion and the expectation of success must be found in the prior art, not in applicants disclosure. *In re Fine*, 5 U.S.P.Q. 2d 1596, 1598 (Fed. Cir. 1988). The Federal Circuit has further stated that "[o]bviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination." *ACS Hospital Systems, Inc. v. Montefiore Hospital*, 732 F2d 1572, 1577 (Fed. Cir. 1984) (footnote omitted, emphasis added).

Neither McMurry, Brixner, Lauffer nor any combination thereof discloses or claims image enhancement that is dependent on the state of the target. Moreover, it is not obvious from the mere binding of an agent to a protein under physiological conditions when and how binding will be affected by therapy that produces changes in the protein or the surrounding tissue. Furthermore, Brixner does not disclose the advantages of using the R_1 relaxivities as a measure of tissue binding (described in detail in the present application, pp. 20-22), and the cited Lauffer reference claims only compounds and compositions. Since the present application recites a monitoring method not directed toward specific contrast agents, Lauffer cannot render the current claims obvious.

Similarly, Vogl discloses only the use of MRI contrast agents for guidance of the laser during thermotherapy. Tissue damage during therapy is predicted from a theoretical calculation based on the temperature and time of exposure to the laser, both of which are completely independent of any monitoring by MRI. Moreover, Vogl uses only an untargeted contrast agent, Magnevist® (p. 730, column 1). The relaxivity of Magnevist® does not change during therapy unlike the present invention which provides the additional advantage that image enhancement depends on the state of tissue being imaged. Therefore the untargeted contrast agent used by Vogl cannot possibly suggest the use of targeted agents to monitor protein denaturation and tissue viability at specific sites.

The substantial decrease in image enhancement (as measured from the corresponding decrease in relaxivity) that occurs with denaturation of the target is large using the current method and non-existent in Vogl (*cf.* Figures 1 and 3 of the application). Therefore Applicants submit that the instant invention is not obvious over any combination of

Brixner, McMurry, and Lauffer irrespective of Vogl since none of these references discloses the property of state-dependent tissue binding or the use of state-dependent tissue binding as a means for monitoring tissue viability and protein denaturation.

In conclusion, no reference or combination of references discloses state-dependent binding or changes in image characteristics during the monitoring of protein denaturation and tissue viability. There is no direction to combine these references with each other or with any other reference. Furthermore, there is no reasonable expectation that successful state-dependent binding or image characteristics could be achieved with any combination of these or other references.

Applicants respectfully request entry of this amendment and an allowance of the amended claims.

Respectfully submitted,

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